



Early Diagnosis and Intervention in Multiple Sclerosis

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Abstract

This article provides guidelines for identifying and treating relapsing-remitting MS in the primary care setting and reviews recent additions to treatment options for disease management. Approaches for patient counseling and recommendations by the National Multiple Sclerosis Society are also discussed.

Suggested citation: Early Diagnosis and Intervention in Multiple Sclerosis. Krupkin Whitney, D. *Int J MS Care* [Serial on-line]. September 2001;3(3).

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of unknown origin that causes multifocal demyelination, axonal damage, and neuronal loss throughout the central nervous system: brain, brainstem, and spinal cord. MS can present with a wide variety of neurologic symptoms. The annual number of MS cases reported in the United States from 1990 through 1992 was 180,000, according to the Centers for Disease Control and Prevention.¹ The National Multiple Sclerosis Society (NMSS) currently reports that between 250,000 and 350,000 Americans have MS.² Women are three times more likely than men to get MS.² Also, MS is disproportionately more common in whites than in people of other races.² The greatest prevalence of MS is in the temperate regions of the globe,² with isolated additional pockets of high prevalence elsewhere, including parts of Australia and New Guinea. An individual's geographic risk is linked to the location where he or she lives during the first 15 years of life.² Onset of MS usually occurs between ages 20 and 40 years. Although there are genetic risk factors,³⁻⁵ MS is not directly inherited. A viral link, environmental factors, or a combination of any or all of these factors may stimulate the pathogenesis of MS.³

While most primary care providers will encounter relatively few patients with MS, as a group they are most likely to be the first to see a patient initially presenting with MS symptoms, according to

the NMSS.⁶ It is likely, therefore, that the primary care physician will be the first to suspect or identify MS. Early diagnosis of MS has become particularly important since disease-modifying therapies have become available.

Relapsing-Relmitting MS

MS can be classified as progressive or relapsing-relmitting.^{4,5} As suggested by the terms, symptoms in progressive forms of MS continue and steadily worsen. Remissions or plateaus can occur, but without total recovery between exacerbations. Progressive MS steadily worsens, with or without superimposed exacerbations. Relapsing-relmitting MS (RRMS) differs in that symptoms appear, remit, and relapse episodically with a stable clinical baseline between exacerbations. In RRMS, there is full or partial recovery between exacerbations, sometimes for extended periods.

RRMS is challenging to diagnose because of the myriad neurologic symptoms with which it can present. MS can mimic and be mimicked by numerous other conditions; hence the differential diagnosis is vast. Once positive diagnostic criteria are fulfilled, MS is confirmed only after a thorough neurologic evaluation eliminates other diseases. If a patient switches physicians, a pattern of exacerbations may be missed entirely.

Symptoms and Diagnosis

Many symptoms occur sporadically, and the same patient may have different symptoms with each exacerbation (Table 1). Unfortunately, there is no typical pattern of exacerbation and no way to predict a patient's likely pattern or prognosis based on symptom manifestation at diagnosis.

Table 1. Symptoms Commonly Associated With MS.

- Weakness in the extremities
- Stiffness and spasticity
- Gait disturbances
- Visual disturbances, including decreased visual acuity, diplopia, and scotomata
- Paresthesias in the extremities, torso, or face
- Balance and coordination impairment
- Bladder or bowel dysfunction
- Sexual dysfunction
- Fatigue
- Cognitive and emotional disturbances
- Pain

Motor weakness in one or more limbs is the most common initial manifestation of MS, occurring in about 40% of patients at the time of diagnosis. The patient may have frank weakness, or may experience the weakness as easy fatigability of the limb, dragging one leg, tripping, or a subjective sensation of stiffness, which is a manifestation of spasticity. The neurologic examination will likely reveal upper motor neuron signs such as spasticity, hyperreflexia, or abnormal reflexes such as the Babinski's or Hoffmann's sign. Lower motor neuron signs such as fasciculations do not result from MS; atrophy, if present, is atrophy of disuse.

Optic neuritis is the presenting manifestation of MS in 22% of patients, with heightened likelihood of progressing to definite MS if white matter lesions are found on magnetic resonance imaging (MRI).

Sensory disturbances constitute the first MS symptoms in 21% of patients. While some may report

actual numbness, the subjective experience is often more subtle, covering the range of hypesthesia, hyperesthesia, dysesthesias, and allodynia. The patient may lack adequate vocabulary to express these sensations or hesitate to report the more bizarre dysesthesias, such as formication. Findings of the neurologic examination will often be benign, but long tract signs, if present, enhance suspicion of MS, and a Lhermitte's sign may be elicited.

Disturbances of extraocular movements are the presenting symptoms of MS in 12% of cases. The patient may report frank diplopia, but may have less florid complaints, such as oscillopsia or vague visual dysphoria, especially when looking at moving objects. Almost any abnormality of extraocular movements may be found on examination, including nystagmus, disconjugate gaze, and internuclear ophthalmoplegia.

Although vertigo is the presenting symptom in only 5% of cases, over time 40% to 50% of MS patients will experience vertigo. Trigeminal neuralgia in an individual younger than 50 years should arouse suspicion of MS, as should recurrent trigeminal neuralgia.

MS presents with bladder disturbances in only 5% of cases, but over time, almost every MS patient will encounter bladder difficulties. These span the range from frank incontinence to complete urinary retention, but a mixed picture is most common, with complaints such as hesitancy, frequency, incomplete emptying, leaking, and frequent urinary tract infections. Urodynamic testing will most often reveal detrusor-sphincter dyssinergia. Bowel complaints often accompany bladder dysfunction, constipation being the most frequent complaint. Absence of any bladder disturbance after 10 years of other neurologic symptoms casts doubt upon a diagnosis of MS.

Fatigue (usually neurogenic fatigue or "lassitude") is a nearly ubiquitous symptom among MS patients. Fatigue may also arise secondary to other neurologic symptoms, such as weakness. Depression, while not a common presenting symptom, occurs as an organic manifestation of MS at some point in the course of the disease in 42% of patients.

A history of two or more episodes of the most common symptoms separated by periods of remission is generally reason to suspect MS.⁷ Diagnosis is indirect and based on clinical and laboratory findings. The directed neurologic examination (Table 2), which takes only a few minutes and can be performed in the office, is designed to evaluate heavily myelinated tracts in the central nervous system. Examination may reveal weakness, spasticity, hyperreflexia, optic pallor, nystagmus, ataxia, or other evidence of central nervous system pathology. While neurologic examination may reveal abnormalities which have not manifested in clinical symptoms, it is nonetheless possible for a person with MS to have a normal neurologic examination early in the course of the disease. In the primary care setting, the directed neurologic examination can enhance suspicion of MS, but it does not establish a diagnosis.

Table 2. Directed Neurologic Examination.

Overview

When a patient's history is suggestive of MS but not conclusive, the neurologic examination can provide important diagnostic information. A directed neurologic examination designed with the "possible MS" situation in mind targets heavily myelinated tracts in the central nervous system to look for evidence of silent lesions. This directed neurologic examination should add no more than two minutes to an office visit.

Cranial Nerves

Fundoscopic examination will reveal optic pallor if there has been a prior attack of optic neuritis. A more subtle finding is the afferent pupillary defect. This finding is elicited by the "swinging flashlight test." A positive test result consists of a paradoxical dilation to light.

Myelinated tracts in the brainstem coordinate extraocular movements, and any disorder of eye movements can conceivably be caused by MS. Frankly disconjugate gaze is easy to spot. Nystagmus is a frequent finding. The "INO" (internuclear ophthalmoplegia) is a specific abnormality of extraocular movements caused by lesions in the median longitudinal fasciculus and is sometimes abbreviated as "MLF." Classic INO involves ipsilateral abduction limitation. There are numerous variants.

Motor Exam

Patients are usually aware of frank weakness but may not be aware of inability to arise unassisted from the squatting position.

Hyperreflexia is a consequence of loss of inhibition from descending motor tracts. The Babinski's and Hoffmann's signs are special examples of loss of inhibition.

Spasticity, which is a disorder of deep tendon reflex loops, is a companion of hyperreflexia. Spasticity is best elicited by passively moving the limbs with the patient as relaxed as possible.

Coordination

Irregular movement, tremor, and past-pointing on finger-nose-finger maneuver or heel-knee-shin maneuver reflect disruption of cerebellar connections.

Gait

The most common abnormal finding in early MS is gait spasticity.

Station

A positive result on Romberg's test would be unlikely in this setting, but inability to stand on one foot may be evidence of abnormal station.

There is no definitive diagnostic test to confirm or exclude MS. Magnetic resonance imaging is the most sensitive noninvasive imaging technique; it will detect demyelinated areas, or plaques, in the brain and/or spinal cord of 95% of patients with definite MS. Actively inflamed areas can be distinguished from old plaques using gadolinium contrast enhancement, as the blood-brain barrier is damaged in active lesions. A normal MRI, by itself, does not rule out MS. Central delays in visual-evoked responses, brainstem auditory-evoked responses, or somatosensory-evoked responses may be caused by demyelination.⁷ These findings, however, are nonspecific and require thoughtful clinical correlation. Cerebrospinal fluid is abnormal in the majority of MS patients,⁴ but normal cerebrospinal fluid does not rule out a diagnosis. The presence of oligoclonal bands, indicating immunoglobulin G synthesis within the blood-brain barrier, is a common finding in MS patients.

While diagnosis is not the responsibility of the primary care physician, it is usually the primary care doctor who is best positioned to recognize early signs and symptoms suggestive of MS and initiate referral to a general neurologist or MS specialist to establish a definite diagnosis, whether of MS or of another neurologic condition.

Intervention

It is generally accepted that onset and progression of MS occur before overt clinical symptoms begin, and progression continues even during periods of apparent remission.^{8,9} Specifically, there is evidence substantiated by MRI and pathologic analysis that MS causes axonal damage even when there are no clinical signs or symptoms of the disease.⁸ Since the disease-modifying effects of immunomodulating agents have been demonstrated, and since disease activity is ongoing between

exacerbations and even prior to the first clinical manifestation, early intervention has become the standard of care, and therapy should not be discontinued during apparent remissions.⁶

Comprehensive management of RRMS includes treating the underlying disease process, minimizing specific symptoms, managing exacerbations, and attending to quality of life for both patient and family.⁷ Until recently, there were no pharmacologic agents that were shown to modify the underlying pathophysiology of MS. There are now three immunomodulating agents approved in the United States for treatment of RRMS, as well as a recombinant interferon beta-1a agent (Rebif[®]) available for use in Europe, Canada, and Australia. In addition, mitoxantrone (Novantrone[®]), an antineoplastic agent, is the one drug approved by the US Food and Drug Administration for the treatment of progressive MS.

The three agents currently available in the United States for treatment of RRMS are interferon beta-1a (Avonex[®]), interferon beta-1b (Betaseron[®]), and glatiramer acetate (Copaxone[®]). Clinical studies indicate that all three of these agents are effective in reducing the frequency and severity of exacerbations and the development of brain lesions, as measured by MRI.¹⁰⁻¹² Interferon beta-1a is administered weekly by intramuscular injection; interferon beta-1b is administered every 48 hours by subcutaneous injection; and glatiramer acetate is administered daily by subcutaneous injection. With proper training in injection technique, patients can self-administer any of these treatments. Most importantly, physicians must help patients understand the necessity of continuing therapy, even during symptom-free periods.

Compliance with injectable medications is a challenge, especially when symptoms are minimal, and side effects present a further challenge to compliance. Close to two thirds of patients using interferon therapy will experience flulike symptoms, sometimes accompanied by low-grade fever, for up to 24 hours following injection. This reaction wanes, and for most patients ceases altogether by the end of three months of treatment. During that time, the flulike symptoms can be blunted by acetaminophen or a nonsteroidal anti-inflammatory drug taken orally before injection and repeated after four to six hours if necessary. Some patients whose flulike side effects are severe and refractory to first-line management will benefit from pretreatment with prednisone 5 mg orally.

Injection site reactions can occur with interferon beta-1b (85% of patients injecting drug vs 37% of those injecting placebo), glatiramer acetate (66% of patients injecting drug vs 37% of those injecting placebo), and, less commonly, with interferon beta-1a. Usually these are minor and resolve spontaneously. Rare cases of infection and tissue necrosis have been reported with interferon beta-1b (5%). Injection site reactions can be minimized by meticulous injection technique, including the use of automatic injection devices. Icing the skin before and after injection may help. Most patients embarking on self-injection of MS treatment receive one or more visits from a home health nurse to teach injection technique and provide support.

Glatiramer acetate injections may be followed within 30 minutes by a systemic reaction variously characterized by facial flushing, chest discomfort, palpitations, and dyspnea, lasting from 30 seconds to 30 minutes. This is a benign and self-limited reaction and was reported by 15.2% of glatiramer acetate recipients and 3.2% of placebo recipients in an extended trial. The reaction occurs unpredictably and irregularly. Of those who experience this reaction, most experience it only once; in others it may recur at wide intervals. Overall, it occurred in about 1 of 840 daily injections in an extended trial.¹³

Leukopenia and elevated transaminases can result from interferon therapy, rarely so profound or so persistent as to require discontinuation of treatment. Complete blood cell count and transaminases should be measured at three-month intervals. Depression, which occurs commonly as a primary symptom of MS, can also be caused by interferon beta-1a on occasion.

Both interferons are classified as Pregnancy Category C; glatiramer acetate is classified as Pregnancy Category B.

Cultivation and regular reinforcement of realistic expectations for therapy contribute positively to compliance. Patients who understand at the outset that immunomodulating agents do not cure MS or reverse neurologic deficits are less likely to discontinue treatment than are those patients who harbor unrealistic expectations.

Intensive corticosteroid therapy is frequently used for acute exacerbations of MS symptoms and can be administered intravenously or orally. Patients should be advised about the potential side effects associated with corticosteroid treatment, such as immune suppression, mood swings, headaches, restlessness, weight gain, and, rarely, aseptic necrosis of the femur and other bones. Corticosteroids should be reserved for short-term therapy only, due to serious adverse effects of long-term use, such as Cushing's syndrome and osteoporosis.

Mitoxantrone, an immunosuppressive antineoplastic agent, has been shown to slow progression of clinical disability in progressive forms (relapsing-progressive and secondary progressive, but not primary progressive) of MS, with corroborative MRI findings. Potential cardiotoxicity excludes patients with cardiac risk factors and limits total lifetime dose. Because of total lifetime dose limits, the timing and duration of treatment are critical. Many neurologists intervene with mitoxantrone to regain disease control in patients whose exacerbations become more frequent or who show accelerated progression in spite of treatment with interferon or glatiramer acetate treatment. In this setting, mitoxantrone is administered intravenously every three months for up to two years. Mitoxantrone is also used in place of methylprednisolone to treat some exacerbations.

Symptom management includes a variety of measures, depending on the symptom. Often, because of the diverse nature of symptoms—ranging from fatigue to bowel or bladder dysfunction—it is advisable to refer the patient to a specialist. See the section titled "Referral to Other Care Providers" for information about treating specific symptoms.

Communicating the Diagnosis to the Patient

With the proliferation of managed care, primary care physicians face increasing restrictions on the amount of time they can spend with each patient. Nevertheless, physician-patient communication may be one of the most important factors affecting treatment compliance and quality of life.⁷

Patients receiving an official diagnosis of MS generally need some extra time beyond the usual office visit to learn about the implications of the diagnosis and the rationale and choices for treatment, as well as to ask questions and begin to process the news. A patient should learn the diagnosis directly from the physician, not by letter or phone or from any other member of the health care team. Sensitivity to the patient's emotions and coping style includes listening to what he or she is and is not asking, and can help the physician tailor the scope and pace of information offered to the patient. Delivering bad news can be painful for both the patient and physician, so being prepared for an emotional response from the patient is important.

In addition to personal communication from the physician, MS patients and their families benefit from written information about the disease, treatments, and available support services. This approach can reinforce the information provided by the physician and help patients think of questions to ask during follow-up visits. Subsequent discussion of treatment options may be more productive if patients have had the opportunity to inform themselves about available therapies in advance.

Involving Patients in Treatment

Physicians should provide patients with information about therapeutic options and, where appropriate, enlist their participation in selecting treatment. Although not all patients will want to be involved in treatment decisions, many will embark on a course of good compliance as a result of collaborating with the physician. Since treatment is intended to last indefinitely or until a better treatment or a cure is found, it is good policy to take into account any patient preferences or lifestyle factors that can affect willingness to adhere to long-term treatment.

Although immunomodulating agents may delay the progression of MS and reduce the frequency of exacerbations, physicians should be certain patients and families understand that these drugs do not cure MS or reverse existing damage. This understanding is important to sustained adherence to treatment. Potential side effects, their likely duration, and their prevention and management should be discussed during the treatment planning phase. Patients should be told what to expect and when to contact the physician.

Referral to Other Care Providers

Most patients who experience MS symptoms will visit a primary care provider first. MS is a complex disease, however, and in most cases will eventually require the participation of one or more specialists and/or other health care providers to address specific needs. In the diagnostic phase, it is advisable to refer the patient to a general neurologist or MS specialist to confirm the diagnosis and initiate treatment.

Although many neurologists can manage most MS symptoms, increasing disability often requires assistance from other specialists. In particular, since bladder dysfunction occurs at some point in the majority of MS patients,⁷ early referral to a urologist is strongly advised. Neurogenic bladder can be asymptomatic while causing irreversible damage to the upper urinary tract. Spasticity, mobility problems, and debilitating fatigue can be addressed by physiatrists and physical therapists, who can use medication, exercise, and behavioral medicine to help MS patients maintain mobility as long as possible.

Depression is a primary symptom of MS and may require treatment by a psychiatrist or psychologist.¹⁴ Finding a mental health specialist who has expertise with chronic disease or disability is advisable, if possible. Family members of MS patients may also benefit from counseling, as MS affects entire families, not just the individual with the disease. This is particularly so since MS usually begins during the most active years of child-rearing and career development.

Although patients with MS will benefit from specialist care, the primary physician plays a vital role in overseeing the patient's general health. Patients with MS might be inclined to see all their health needs in terms of their neurologic disease and neglect health maintenance responsibilities such as cholesterol and blood pressure management, Papanicolaou smears, or mammograms. The primary care physician is in a unique position to be aware of all aspects of the MS patient's care and quality of life.

MS Support Organizations

Organizations such as the NMSS, the Consortium of MS Centers, and Rehabilitation in MS provide reliable information for anyone interested in learning about MS. Through support groups, patients can interact with others who have MS and find valuable information about the disease itself, treatments, insurance issues, government policies, lifestyle concerns, and much more. Many support organizations advocate in the arena of public health policy, as well, providing a voice for issues that affect MS patients, their families, and providers. Physicians may wish to include contact information for support organizations in the written materials they provide to patients upon

diagnosis.

Advocacy for MS Patients

The NMSS published a Disease Management Consensus Statement for RRMS.⁶ This Consensus Statement is based on current clinical data regarding optimum treatment for MS and is intended for providers, insurers, and patients. The purpose of the Consensus Statement is to educate everyone who has an interest in or a need to know about the treatment of MS and to establish clear objectives for optimal therapy.

The Consensus Statement emphasizes the need for early intervention with one of the three immunomodulating agents currently indicated for the treatment of RRMS. In addition, the NMSS strongly advocates full flexibility in the selection and reimbursement of these three agents. Formularies should not limit physicians' choices to only one or two agents because the agents act by different mechanisms, and no single agent will be effective and tolerable for all patients.

Other objectives of the Consensus Statement are to dispel misinformation that these therapeutic options are experimental and to reinforce the idea that patients with relapsing forms of MS, regardless of their level of disability, age, or frequency of exacerbation, should have access to all available treatments. The absence of exacerbations, which is a desirable result of therapy, should not prompt a patient to discontinue therapy. Familiarity with the NMSS's Consensus Statement recommendations can provide a framework for primary care physicians who are unfamiliar with recent trends in the treatment of RRMS.

Conclusion

Primary care physicians play a key role in identifying the early signs of RRMS. Prompt diagnosis allows early intervention with disease-modifying agents which can reduce the frequency and severity of exacerbations, slow the accumulation of MRI lesion burden, and delay the development of disability. Treating the underlying disease can proceed concurrently with symptom management and psychosocial interventions.

Finally, ongoing education and sensitive communication with the patient may improve adherence to treatment. Because continued treatment with an immunomodulating agent is the only current option for sustained treatment to slow disease progression, it is essential for patients to understand how to self-administer injections and otherwise take an active role in their own care. A multidisciplinary approach is necessary at times in order to provide the best care for the patient. Primary care physicians are encouraged to refer to the NMSS Consensus Statement for more information about the care of patients with RRMS.

Acknowledgments

Content for this article was drawn from insights provided by a group of physicians and allied health professionals who have been diagnosed with MS. Their unique perspective as both providers and patients was particularly valuable in forming recommendations about patient communication and involvement. These contributors include: Margo Benner, RN; Suman Hariharan, MD; Elisabeth Heininger, RD; Nancy Holland, RN, EdD; Roger M. Katz, MD; Mark Levinson, MD; Mary Madsen, RN; Carol Matthews, MSN, CFNP/CPNP; David A. Reich, MD; Susan M. Reynolds, RN; Susan Roys, RN, BSN; and Cindy Wright, RN. The author also wishes to acknowledge Catherine Jarrell for her assistance in preparing this article. This work was supported by an unrestricted grant from Teva Marion Partners.

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